

## **REMARKS**

The Office Action dated January 21, 2010 rejected claims 138-140, 142-162, 164-189, and 211-260. Claims 190-210 have been withdrawn from consideration. Claims 1-137, 141 and 163 have been canceled. The action has been marked final by the Examiner. Please consider these remarks after final rejection. Applicants submit that thoughtful consideration of these remarks and the substance of the cited art make it appropriate and proper to issue a notice of allowance for all the pending claims in this application.

### Anticipation Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 138-140, 142-144, 151, 153, 165-170, 177, 179, 211-216, 223, 225, 236-241, 248 and 250 under 35 U.S.C. § 102(b) as being allegedly anticipated by Wright IV et al. U.S. Patent Application Pub. No. 2003/0044458 (hereinafter referred to as “Wright”). Applicants respectfully traverse.

The instant application claims in independent claim 138:

A unit dose of a controlled release pharmaceutical formulation, wherein said formulation comprises melt extruded multiparticulates comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

The instant application claims in independent claim 166:

A plurality of a controlled release granulates comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

The instant application claims in independent claim 211:

A plurality of controlled release melt extruded multiparticulates comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

The instant application claims in independent claim 236:

A controlled release pharmaceutical formulation comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

To be clear, in claims 138, 166, 211 and 236, as well as the claims that depend on them, the claimed formulations comprise melt extruded multiparticulates. The melt extruded multiparticulates must comprise a rubbery matrix including neutral poly(ethyl acrylate, methyl methacrylate) copolymer, and an active agent (emphasis added).

We respectfully submit that, contrary to the Examiner's assertion, Wright does not disclose the formulation according to the present invention comprising melt extruded multiparticulates which comprise a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, and an active agent. Consequently, contrary to the Examiner's assertion, claims 138-140, 142-144, 151, 153, 165-170, 177, 179, 211-216, 223, 225, 236-241, 248 and 250 are novel over the disclosure of Wright. Applicants will make this point clear in the following detailed remarks.

As we noted in our previous instructions, Wright discloses a dosage form comprising a first composition and a second composition. The first composition comprises a therapeutic agent and the second composition comprises an adverse-effect agent (paragraph [023]). The composition provides tamper resistance by releasing the adverse-effect agent if it is tampered

with, *e.g.* chewed, crushed, ground or dissolved (paragraph [029]). In contrast, when the composition is taken orally as intended only the therapeutic agent is released. This is achieved by the use of specific coatings on the first and second compositions that render the first composition soluble in the stomach but the second composition insoluble (unless tampering occurs). This is explained fully at paragraph [028].

Paragraph [030] of Wright states that the first composition may be designed to provide slow release of the therapeutic agent to the patient. This may be achieved by using a sustained release coating (section 5.4.4) or by dispersing the therapeutic agent in a controlled release matrix (paragraph [082]). This is crucial to recognize because it is one of the keys to understanding why Wright does not disclose the unit dose of a controlled release formulation according to the claim of 138 of the instant application.

The discussion of the composition of the controlled release matrix starts at paragraph [084] and is relevant because it is within these passages that the only mention is made of the possible use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, particularly Eudragit NE 30 D. Paragraphs [085-087] of Wright set out three classes of polymers that may be used in a controlled release matrix, namely (a) hydrophilic or hydrophobic polymers, (b) digestible, long chain hydrocarbons or (c) polyalkylene glycols. Paragraph [088] then goes on to say that a suitable matrix comprises one or more cellulose ethers or acrylic resins, one or more aliphatic alcohols and/or one or more hydrogenated vegetable oils. Examples of acrylic resins are set out in paragraph [089] and one of the seven mentioned is Eudragit NE 30 D.

Wright also discloses at paragraph [084] that the therapeutic agent can be dispersed in the matrix using dry or wet granulation or by blending. Paragraph [092] elaborates further and states that the controlled release matrix containing the therapeutic agent can be prepared

using conventional techniques including melt granulation, wet granulation, dry blending, dry granulation or co-precipitation. There is no mention of melt extrusion.

Finally, the first paragraph on page 11 of the January 21, 2011 office action refers to paragraph [094] of Wright. It should be understood that paragraph [094] of Wright refers to the preparation of the first and second compound for the coating process, i.e. the alternative sustained release method (i) above. Paragraph [094] states that the first (and second) composition is a solid such as fine granules, pills, beads, capsules, tablets or powders. The solids are said to be made by means known in the art. The typical materials used to prepare them are set out in paragraph 94. There is no disclosure at any point in this paragraph that a neutral poly(ethyl acrylate, methyl methacrylate) copolymer such Eudragit NE 30 D could or should be used, nor would the skilled person have been given any incentive to consider the use of such a material on the basis of this disclosure.

It is noted that it is stated in the last sentence of Paragraph 94 that the solid compositions can be prepared by various conventional methods known in the art, including melt extrusion. Applicants further note that the Examiner has referred to this in his rebuttal of their arguments in response to the previous non-final Office Action. Applicants respectfully submit that the Examiner has misinterpreted the disclosure of Wright. The reference to the use of melt extrusion is only in the context of the preparation of solid compositions prior to the coating process (see Paragraphs 95 to 97). When formulations of Wright are prepared by dispersion in a controlled release matrix, there is no disclosure or suggestion that multiparticulates should be prepared using melt extrusion.

Applicants submit, therefore, that the Examiner's arguments actually (and no doubt accidentally) impermissibly combine separate parts of the disclosure of Wright to arrive at the presently claimed invention. These separate parts of the disclosure relate to completely

different and distinct embodiments of Wright. It is respectfully submitted a rejection under 35 U.S.C. § 102(b) cannot be formulated by selecting unrelated parts of the disclosure and make a collection of these to arrive at the present invention. The mention that the preparation of multiparticulates that may comprise an acrylic resin that may be a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, particularly Eudragit NE 30 D, comes in the context of the dispersion of a therapeutic agent in a controlled-release matrix in Wright, (paragraphs 82 to 92). The mention to the use of melt extrusion comes only in the context of the preparation of solid first and second compositions that may be multiparticulates that may be prepared by melt extrusion in which the solid compositions are coated with layers of a desired coating such as the sustained-release coating.

Therefore, Applicants respectfully submit that Wright does not anticipate independent claim 138, 166, 211 or 236 because there is simply no disclosure in Wright of a unit dose or a a controlled release pharmaceutical formulation comprising melt extruded multiparticulates that comprise a neutral poly(ethyl acrylate, methyl methacrylate) copolymer or a plurality of melt extruded multiparticulates that comprise a neutral poly(ethyl acrylate, methyl methacrylate) copolymer. Rather, Wright discloses a first composition that may be in the form of granules and may contain Eudragit NE 30 D but which is prepared by melt granulation, wet granulation, dry blending, dry granulation or co-precipitation. There is no disclosure whatsoever of melt extrusion. Since every element of independent claims 138, 166, 211 or 236 is not disclosed in Wright, the reference cannot anticipate claim 138, 166, 211 or 236, nor any claim which is dependent upon either claim 138 166, 211 or 236.

Applicants note that the Examiner has questioned the relevance of the specific reference in the previous response to the fact that EUDRAGIT NE 30 D is not stated to be a particularly preferred polymer in Wright on the grounds that none of the claims of the instant

application are directed to this copolymer. Applicants offer the below explanation of the importance of EUDRAGIT NE 30 D in understanding the difference between of the disclosure of Wright and the instant claims.

As noted above, the only disclosure in Wright of the use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer is the reference to the use of EUDRAGIT NE 30 D. This is listed in paragraph 89 as an example of a possible acrylic resin that may be used in the preparation of the controlled release matrix formulations of Wright (see paragraphs 82 and 88 also). Thus, the controlled release formulations of Wright only refer to one neutral poly(ethyl acrylate, methyl methacrylate) copolymer, EUDRAGIT NE 30 D, and then only in the context of controlled release matrix formulations that are not, as explained above, melt extruded multiparticulates as required by claims 138, 166, 211 or 236 of the present invention. Although not directly relevant to the novelty of the present invention, there is no suggestion in Wright that EUDRAGIT NE 30 D is a preferred material for use in preparing the controlled release matrix of the controlled release formulations of this reference. This is supported by consideration of the examples, none of which employ it.

Applicants also note that the Examiner has questioned the assertion in the previous response that if a person skilled in the art attempted to derive the present invention as recited in claim 138 from Wright he would have to choose 2 of 5880 possible unit doses disclosed by the various lists therein. In actual fact, the reality is worse than that. It is simply not possible to arrive at the present invention from the disclosure of Wright no matter what specific selections are made. However, we are happy to set out the exact means by which we arrived at this calculation.

Further, with respect to all of the claims, it is submitted that Wright is not an anticipatory reference because Wright's disclosure does not describe the presently claimed

invention sufficiently to have placed a person of ordinary skill in the field in possession of the invention. *See, In re Spada*, 911 F.2d 705, 708 (Fed.Cir 1990). Notably, Wright begins the discussion of controlled release matrices by stating that “[a]ny controlled-release matrix can be used in the oral dosage form of the invention” (paragraph [082] ). The presently claimed novel combination of elements are certainly not disclosed together anywhere in Wright. However, even the closest approximation of claim 138, arguably the pending claim with the fewest limitations, the person of ordinary skill would have had to at least make each of the following selections from the disclosure of Wright:

1. decide to make the first composition a slow release composition (1 choice from 2);
2. decide to provide slow release by use of a matrix rather than a coating (1 choice from 2);
3. decide to use a class (a) polymer in the matrix (1 choice from 3);
4. decide to use an acrylic polymer in the matrix (1 choice from 10);
5. decide to use Eudragit NE 30 D as the acrylic polymer (1 choice from 7);
6. decide to formulate the first composition as granules or fine granules (2 choices from 7); and
7. decide to prepare the first composition by melt extrusion (not disclosed).

Hence to arrive at the unit dose of claim 138 from Wright, the person of ordinary skill would have had to choose 2 of 5,880 possible unit doses disclosed by the various lists therein ( i.e. multiply the positive options  $(1 \times 1 \times 1 \times 1 \times 1 \times 2 = 2)$  out of the total number of possibilities  $(2 \times 2 \times 3 \times 10 \times 7 \times 7 = 5880)$ . Even then, however, the skilled person does not

arrive at the present invention as recited in claim 138. This is because there is no disclosure in Wright of the preparation of the controlled release composition as a melt extruded multiparticulate. Thus, at the priority date of the present application, the skilled person in attempting to arrive at the formulation of the present invention, would have had to make a selection of 2 options out of a possible 5880 possible unit doses disclosed in Wright, to get to the closest approximation of claim 138. Even then the skilled artisan still would not have arrived at the invention as claimed. A similar analysis applies to independent claim 165, as well as new independent claims 211 and 236. Therefore, the very broad disclosure of Wright cannot qualify as an anticipatory disclosure of the present claims under 35 U.S.C. § 102(b). “[A]lthough specific claims are subsumed in [a prior art reference’s] generalized disclosure ..., this is not literal identity” required for anticipation. *See, Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559 (Fed. Cir 1992) Similar to the *Minnesota Mining* case, the cited reference’s ranges were “so broad as to be meaningless” and provided no guidance on how to construct a product with the claimed invention’s beneficial properties.

It is respectfully submitted that the subject matter of all claims of the instant application, including claims 138-140, 142-144, 151, 153, 165-170, 177, 179, 211-216, 223, 225, 236-241, 248 and 250 that currently stand rejected by the Examiner are novel over the disclosure of Wright. Applicants respectfully submit it is clear from the above arguments and explanations that, contrary to the Examiner's assertion, there is no disclosure of formulations according to the presently claimed invention in Wright. On the contrary, the Applicants have convincingly shown the rejection under 35 U.S.C § 102(e) is a combination of separate, unrelated disclosures brought together out of context to arrive at the instant claims of the Application. This collocation of separate pieces of information does not, of course, represent an enabling disclosure of the invention. At no point is there a disclosure of the key

requirement of the formulations of the present invention, particularly melt extruded multiparticulates comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent. Therefore, it is respectfully submitted that the present claims are not anticipated by Wright.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 138-140, 142-162, 164-189, 211-260 under 35 U.S.C. § 103(a) as being unpatentable over Wright in view of Oshlack et al. U.S. Patent No. 5,958,452 (hereinafter “Oshlack ‘452) and Oshlack et al. U.S. Patent Application Pub. No. 2002/0010127 (hereinafter “Oshlack ‘127). Applicants respectfully traverse.

Applicants and the Examiner agree that Wright is not anticipatory for claims 145-150, 152, 154-162, 164, 171-176, 178, 180-189, 217-222, 224, 226-235, 242-247 and 249. Applicants have made clear above Wright is not anticipatory for claims 138-140, 142-144, 151, 153, 165-170, 177, 179, 211-216, 223, 225, 236-241, 248 and 250. The main points of the above argument can be summarized as follows:

- (i) that Wright teaches how to prevent a user wanting to administer a dosage form that has been tampered with, rather than how to prevent tampering in the first place; and
- (ii) that Wright et al only lists Eudragit NE 30 D as one of many possible controlled release matrix agents and does not teach that it imparts tamper resistance to melt extruded multiparticulates.

Applicants do not believe that lesser requirements of an obviousness rejection under 35 U.S.C. § 103(a) overcome the deficiencies pointed out above for Wright in the traverse of anticipation. It is not obvious to use the teachings of Wright to thwart the physical acts of tampering (e.g. grinder/crushing), also it is not obvious from Wright alone to use any neutral

poly(ethyl acrylate, methyl methacrylate) copolymer, including Eudragit NE 30 D, in a controlled release matrix to prevent tampering. Therefore, Wright alone is not anymore suitable to support a 103(a) rejection for any of the instant claims than it is to support a 102(e) rejection for any given claim.

The tamper resistance of the present invention significantly diminishes the likelihood that a person seeking to abuse the dosage form by grinding/crushing followed by solvent extraction and/or direct solvent extraction would be able to obtain a sufficient amount of the active agent from the dosage form to abuse.

In contrast thereto, Wright seeks to obtain a totally different kind of tamper resistance. Specifically, Wright does not aim to make its dosage forms more resistant to crushing, grinding or extraction, rather it aims to prevent a user from achieving a euphorogenic or pleasing effect if a dosage form is administered after crushing, grinding or dissolving. As discussed in detail in paragraph [028] of Wright, this is achieved by including an adverse-effect agent in its dosage form which is released only if the dosage form is tampered with.

The direction and aim of present invention and Wright are therefore entirely different. Correspondingly, Wright does not contain any teaching or suggestion whatsoever as to how to produce unit doses, granulates, multiparticulates or formulations that have improved resistance to abuse by grinding or crushing followed by solvent extraction and/or direct solvent extraction. Certainly, Wright does not contain any teaching that these properties are provided by the inclusion of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the matrix. Rather, as discussed above with respect to the anticipation rejection, Wright only mentions the possible use of Eudragit NE 30 D (the only neutral poly(ethyl acrylate, methyl methacrylate) copolymer referred into in the discourse of Wright) in passing among a multitude of possible matrix components. Wright does not mention Eudragit NE 30 D in

connection with any tamper resistance properties. In fact, Wright explicitly states that “[a]ny controlled-release matrix can be used in the oral dosage form of the invention” (paragraph [082] ). Moreover, none of the Examples of Wright utilize a neutral poly(ethyl acrylate, methyl methacrylate) copolymer. A reference such as Wright which discloses a “vast number” of possibilities and provides examples which are different from the presently claimed invention does not provide the requisite motivation or rationale to select a neutral poly(ethyl acrylate, methyl methacrylate) copolymer for inclusion in the matrix. *See, In re Baird*, 16 F3d. 380 (Fed.Cir. 1994).

At the priority date of the present application, the skilled person would have been provided with no teaching or motivation to produce the formulations of the present invention, let alone that by doing so the resulting formulations would have tamper resistance properties.

As a demonstration of the tamper resistance properties, we draw the Examiner's attention to Examples 10 to 13 of the present application and Figure 5, which demonstrate clearly that attempts at extraction of oxycodone HCl via different means from four different formulations of the present invention led to impressive tamper resistance to attempted extraction by crushing and grinding followed by solvent extraction.

At the priority date of the present application, the skilled person would have been provided with no teaching or motivation by the disclosure of Wright to produce the formulations of the present invention, let alone that by doing so the resulting formulations would have tamper resistance properties. There is no reason that the skilled person would have been motivated to combined the disclosure of Wright with Oshlack ‘452 or Oshlack ‘127 as the object of Wright and the means by which it is achieved (tamper resistance by including an adverse-effect agent in its dosage forms that is only released if the dosage form is abused) is different to Oshlack ‘452 (sustained release formulations obtained by melt

extrusion; no disclosure or suggestion of tamper resistance properties); and Oshlack '127 (controlled release dosage forms containing an opioid agonist and antagonist and a controlled release material, in which the antagonist is released at a rate effective to attenuate side effects of the opioid; no reference to use for tamper resistance).

Therefore, it is respectfully submitted that at the priority date of the present invention, a person of ordinary skill in the art would not be taught the invention as recited in the instant claims of the present application by the disclosure of Wright. Furthermore, he would not have been motivated to have combined this document with Oshlack et al (US'452) and/or Oshlack et al (US 2002/'127), as they are related to different problems. Even if he had done so, he would still not have arrived at the subject matter of the instant claims, nor would he have had any reason to believe that the formulations of the present invention would have tamper resistance to crushing, grinding and extraction as discussed and exemplified in the present application.

It is therefore submitted that a person of ordinary skill would not have deduced the presently claimed invention from the general disclosure of Wright regarding various possible matrix ingredients. Further, neither the cited Oshlack '548 nor the cited Oshlack '127 provide any motivation or rationale for selecting a neutral poly(ethyl acrylate, methyl methacrylate) copolymer for inclusion in a unit dose, granulate, multiparticulate or formulation as presently claimed. Accordingly, it is submitted that the presently claimed invention would not have been rendered obvious by the cited references, and withdrawal of the obviousness rejection is respectfully requested.

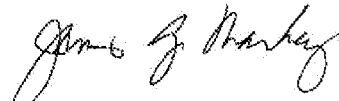
## **Conclusion**

It is respectfully submitted that as the independent clasims are novel and inventive as already demonstrated above, the Examiner's arguments relating to the dependent claims are also unsustainable. First, there would have been no motivation to combine these documents, for the reasons discussed above. Second, even if the skilled person had combined these documents at the priority date of the invention he would still not have arrived at the invention as recited in any one of the claims currently pending, nor would he have had a reasonable expectation that the formulations of the present invention would have the excellent tamper resistance to crushing, grinding and extraction as discussed and exemplified in the present application.

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance, notification of which is respectfully requested. The Examiner is invited to call the undersigned attorney at (516) 874-4250, if a telephone call could help resolve any remaining items.

Respectfully submitted,

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## **EXHIBIT A**

Melt-extruded multiparticulates were produced with the following formulations:

Material	Batch No. (% w/w)	
	F784/53A	F784/26A
Oxycodone HCl	30	30
Ethyl cellulose N10	20	26
Eudragit NE 40 D*	36	30
Stearyl alcohol	12	12
Glycerol dibehenate	2	2
Total	100	100

\*Value stated in solids content only. Liquid dispersion weight is (value/40)x100.

Batch samples were tested as follows:

133 mg of the multiparticulates were subjected to grinding in a mortar and pestle with 24 rotations of the pestle and the product placed in 900 ml water at 37°C for 45 minutes. The amounts of oxycodone dissolved were then determined by HPLC and detection by UV at 210 nm wavelength. The results are presented in the table below.

	F784/53A	F784/26A
% oxycodone released from intact multiparticulates	25.52	24.16
% oxycodone released from ground multiparticulates	56.64	62.46
Difference	31.12	38.30

In the table below, these results are correlated with the formulations of each of the batches.

Material	Batch No. (% w/w)	
	F784/53A	F784/26A
Eudragit NE 40 D*	36	30
Difference in % oxycodone released	31.12	38.30

\*Value stated in solids content only. Liquid dispersion weight is (value/40)x100.